LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Sinupret, coated tablet
Sinupret Forte, coated tablet
(*Gentiana lutea* L., dried root, powder,
***Primula* spp., dried flower, powder,**
***Rumex* spp., dried herb, powder,**
***Sambucus nigra* L., dried flower, powder,**
***Verbena officinalis* L., dried herb, powder.)**

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This module reflects the scientific discussion for the approval of Sinupret and Sinupret Forte. The procedures were finalised at 30 April 2012. For information on changes after this date please refer to the module 'Update'.

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LAY SUMMARY

The Medical Products Agency (Läkemedelsverket, MPA) has granted Bionorica SE, Neumarkt, Germany marketing authorisations for the herbal medicinal products Sinupret, coated tablets and Sinupret Forte, coated tablets. Sinupret Forte contains twice as much as Sinupret of each active substance and each excipient. The products are available without prescription and can be bought from pharmacies and other outlets.

Sinupret has an extensive medicinal use in the EU against sinusitis. The active ingredients are five different powdered drugs: *Gentiana lutea*, dried root, *Primula spp*., dried flower, *Rumex spp*., dried herb, *Sambucus nigra*, dried flower and *Verbena officinalis*, dried herb.
The applicant has submitted a clinical study to demonstrate the clinical efficacy and support the medicinal use. Evidence of clinical safety has also been submitted.

The chemical/pharmaceutical quality of the product is acceptable and no new or unexpected safety concerns have been identified during the assessment. It was therefore decided that Sinupret and Sinupret Forte could be granted marketing authorisations as herbal medicinal products.

I. INTRODUCTION

Bionorica SE, Neumarkt, Germany, has applied for a marketing authorisation for Sinupret and Sinupret Forte, coated tablets. The applications were submitted under Article 10a Well-established use application of the Directive 2001/83 EC, as amended. The applications are national applications for Sweden only.

The active substances are a mixture of powdered herbal drugs: dried root of *Gentiana lutea*, dried flower of *Primula* spp., dried herb of *Rumex* spp., dried flower of *Sambucus nigra* and dried herb of *Verbena officinalis.*

For approved indications, see the Summary of Product Characteristics (SmPC).

Sinupret and Sinupret Forte, coated tablets, were first authorised as natural remedies in 2001 and 2005 respectively. As a consequence of the new legislation regarding (traditional) herbal medicinal products the products were reclassified as herbal medicinal products in 2012.

II. QUALITY ASPECTS

II.1 Introduction

Sinupret and Sinupret Forte are presented in the form of coated tablets. Sinupret contains 6 mg of powdered *Gentiana lutea* root and 18 mg each of *Primula* spp. flower, *Rumex* spp. herb, *Sambucus nigra* flower and *Verbena officinalis* herb.

Sinupret Forte contains exactly twice as much as Sinupret of each active substance and each excipient.

The excipients are: sucrose, talc, lactose monohydrate, calcium carbonate, potato starch, maize starch, dextrin, anhydrous colloidal silica, stearic acid, titanium dioxide, liquid glucose, gelatin, quinoline yellow, indigo carmine, shellac, magnesium oxide, sorbitol, basic butylated methacrylate copolymer, montan glycol wax, povidone, refined castor oil and anhydrous sodium carbonate.

The tablets are packed in blisters.

All manufacturers involved in the production operate in accordance with EU-GMP, or where relevant GACP (Good Manufacturing Practice respectively Good Agricultural and Collection Practice).

II.2 Drug Substance

The herbal substances are:

1. *Gentiana lutea L.*, radix, dried root (gentian, Swedish name: gullgentiana). The substance has a monograph in the European Pharmacopoeia.
2. *Primula veris* L. and/or *Primula elatior* (L.) Hill., flos, dried flowers (primula spp, Swedish names: gullviva and lundviva, respectively). A monograph for the roots of the same plants is included in the European Pharmacopoeia, but the manufacturer uses an in-house specification to control the quality of the flowers.

3. *Rumex acetosa* L., *R. acetosella* L., *R. obtusifolius* L., *R. patientia* L., *R. crispus* L. and/or *R. thyrsiflorus* Fingerh., herba, dried leaves and upper stems (sorrel spp, Swedish names: ängsyra, bergsyra, tomtskräppa, spenatskräppa, krusskräppa and stor ängsyra, respectively). There is no monograph in the European Pharmacopoeia; hence an in-house specification is used.
4. *Sambucus nigra* L., flos, dried flowers separated from the inflorescences (elder, Swedish name: fläder). The herbal substance is covered by a monograph in the European Pharmacopoeia.
5. *Verbena officinalis* L., herba, dried leaves and upper stem segments (verbena, Swedish name: järnört). The herbal substance is covered by a monograph in the European Pharmacopoeia.

All herbal substances are collected (both wild and cultivated) in Europe.

Relevant information on growing conditions and controls of the herbal substances has been presented. The manufacturing process has been adequately described and satisfactory specifications have been provided for starting materials.

The specifications for the active substances include relevant tests and the limits for impurities have been justified. The analytical methods applied are suitably described and validated.

II.3 Medicinal Product

Sinupret and Sinupret Forte are formulated using excipients described in the current European Pharmacopoeia, except for the colourants “green laquer” and “yellow green-light L laquer” (both consisting of indigo carmine and quinoline yellow) which are controlled by an in-house specification and montan glycol wax as well as refined castor oil which have monographs in DAB (official German pharmacopoeia).
All raw materials used in the products are of vegetable origin except lactose monohydrate and gelatin. Lactose monohydrate is derived from milk sourced from healthy animals under the same conditions as milk collected for human consumption.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life and storage conditions claimed in the SmPC.

III. NON-CLINICAL ASPECTS

III.1 Introduction

A thorough literature review has been submitted, in accordance with the requirements for herbal medicinal products submitted under Article 10a Well-established use application of the Directive 2001/83 EC, as amended. The literature relates to the fields of non-clinical pharmacology and toxicology of the Sinupret products and their active ingredients.

III.2 Toxicology

Single-dose toxicity studies in mice, repeat-dose toxicity study in rats (13 weeks) and reproductive and developmental toxicity studies in rats and rabbits have been conducted and the results did not raise any safety concern.

Concerning genotoxic potential, the following product specific studies were conducted: Ames test with and without metabolic activation, mouse micronucleus test and unscheduled DNA synthesis assay. Furthermore, a micronucleus test and Ames test (not complete) were performed on urine from mice treated with Sinupret.
Sinupret may be considered to be non- mutagenic in the tests performed.

The inactive ingredients in Sinupret are common pharmaceutical and/or food ingredients and are not considered to pose any risk.

III.3 Ecotoxicity/environmental risk assessment

Sinupret and Sinupret forte are herbal medicinal products. According to “Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00), (traditional) herbal medicinal products are exempted from the obligation to present an environmental risk assessment due to the nature of their constituents.

III.4 Conclusion on the non-clinical aspects

The information supplied supports medicinal use of the products. No serious safety concerns have been identified.

IV. CLINICAL ASPECTS

IV.1 Introduction

A thorough literature review has been submitted, in accordance with the requirements for herbal medicinal products submitted under Article 10a Well-established use application of the Directive 2001/83 EC, as amended. The literature contains a systematic review of clinical data from treatment of sinusitis with Sinupret.

The documentation for Sinupret forte, coated tablets is the same as for Sinupret, coated tablets.

IV.2 Pharmacokinetics

There are no studies concerning pharmacokinetics. The lack of pharmacokinetic data is acceptable since constituents responsible for the therapeutic effect of Sinupret are not known, and thus pharmacokinetic studies are not possible/relevant.

IV.3 Pharmacodynamics

At present, it is not possible to designate a particular substance to the therapeutic effect with certainty. The mechanism of action cannot be considered clarified. It appears likely that the overall effect of Sinupret depends on several substances and mechanisms.

IV.4 Clinical efficacy

The pivotal study in order to demonstrate efficacy of Sinupret for the approved indication is a randomized, placebo-controlled, double-blind study performed by Neubauer and März (1994). In addition to treatment with an antibiotic and a decongestant, 160 young men with mainly acute sinusitis were treated with either Sinupret 2 tablets 3 times daily (81 patients) or placebo (79 patients) for 14 days. The dosage corresponds to Sinupret forte 1 tablet 3 times daily. Primary end-points were radiographic findings and patient assessment. At the end of therapy, results significantly in favour of Sinupret appeared for both these variables. Results for secondary end-points showed superior results for mucosal swelling, obstruction of sinus drainage and headache. The results of this study have been brought forward in two reviews published.

It is the Medical Products Agency´s opinion, that the study is of sufficient quality to substantiate efficacy in addition to more than 10 years of wide-spread medicinal use in the EU, making approval as a well-established herbal medicinal product according to Article 10 (a) of Directive 2001/83/EC as amended possible. The MPA came to the conclusion that the study results can be interpreted as being valid also without concomitant treatment with an antibiotic and a decongestant.

IV.5 Clinical safety

A large number of patients, children as well as adults, have been exposed to Sinupret in clinical trials but above all through extensive sales of the product in the European Union. The clinical safety documentation as well as the non-clinical safety documentation indicates a low toxicity and absence of frequent adverse effects of the product. For details, the reader is referred to the SmPC.
There have been isolated reports of serious adverse cutaneous events such as erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis in patients treated with Sinupret. Any such adverse reactions should without delay be reported to the MPA.

IV.6 Discussion on the clinical aspects

Sinupret has been approved as a natural remedy in Sweden since 2001. During this time there have been no sales restrictions, i.e. no prescription has been required and sale has been permitted also outside pharmacies. No new risks have been identified that would motivate a different sales status of the product.

V. PRODUCT INFORMATION

The product information (Summary of Product Characteristics, Package Leaflet and labelling) has been assessed and accepted by the Medical Products Agency.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The results of one clinical study of sufficient quality in addition to more than 10 years of wide-spread medicinal use in the EU, make approval as a well-established herbal medicinal product according to Article 10 (a) of Directive 2001/83/EC as amended possible. No signals of serious clinical safety concern have been identified despite an extensive use of Sinupret. Therefore the benefits of Sinupret and Sinupret forte should outweigh the potential risks.

The benefit/risk ratio is considered positive and Sinupret, coated tablets and Sinupret forte, coated tablets are recommended for approval.

VII. APPROVAL

Sinupret, coated tablets and Sinupret forte, coated tablets were approved in the national procedure on 2012-04-30.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
Change in colouring agent Quinoline yellow (E104) is replaced by a combination of riboflavin (E101), copper chlorophyllin and indigotine. Povidone, anhydrous sodium carbonate was removed from the composition. Aluminium hydroxide was added (content of indigotine preparation)		Yes		2015-08-07 2015-09-07	Approval	No

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